2006 Electric Utility Environmental Conference

The Susceptible Population for Environmental Mercury

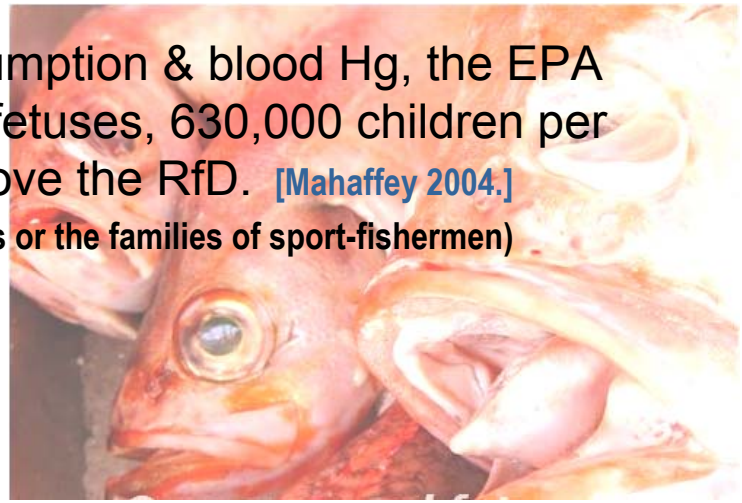
Sid Nelson Jr., Sorbent Technologies Corp.

James B. Adams, Ph.D.
Professor of Chemical & Materials Engineering
Arizona State University (ASU)

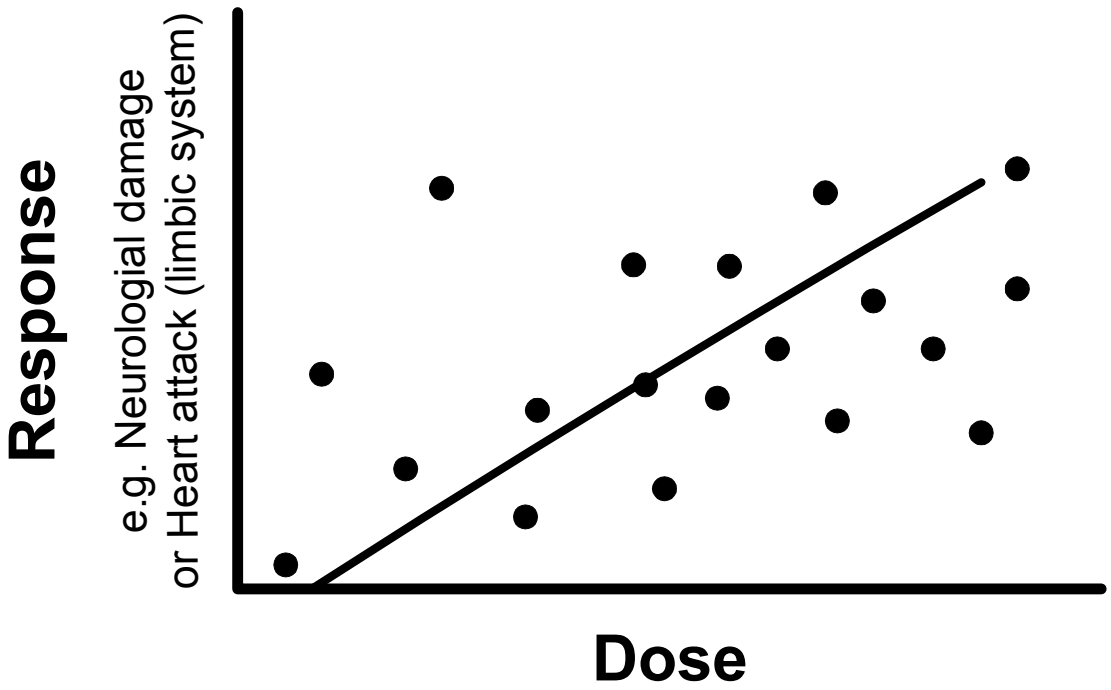
Lead author of DAN! Consensus Report on Treatment Options for Mercury Toxicity

How Much Mercury is Safe?

- 2001 EPA Reference Dose for MeHg: 0.1 µg/kg body-weight/day
- RfD is “an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” **[EPA IRIS definition.]**
- The EPA primarily based its MeHg RfD determination on neurological test results of Faroe Island (& New Zealand) children, associated with MeHg levels in umbilical cord blood. **[U.S. EPA 2001.] [Rice 2004.]**
- From NHANES survey data on fish consumption & blood Hg, the EPA recently reported that about 16% of U.S. fetuses, 630,000 children per year, have mothers exposed to MeHg above the RfD. **[Mahaffey 2004.]**
  (much higher in some subpopulations, like Asian-Americans or the families of sport-fishermen)



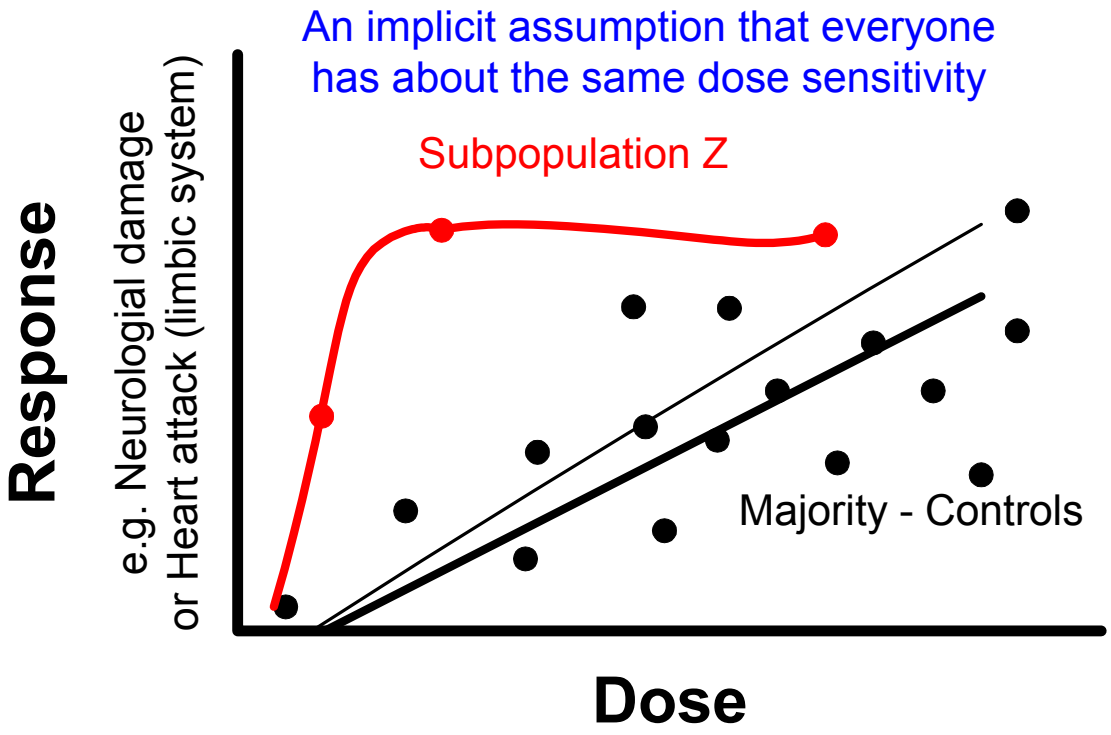
Analytical Structure of the Determination



e.g. Cord blood Hg or maternal hair Hg -
proxy for MeHg injested during pregnancy

(Data is theoretical, for illustrative purposes.)

What If Really Two Separate Populations?



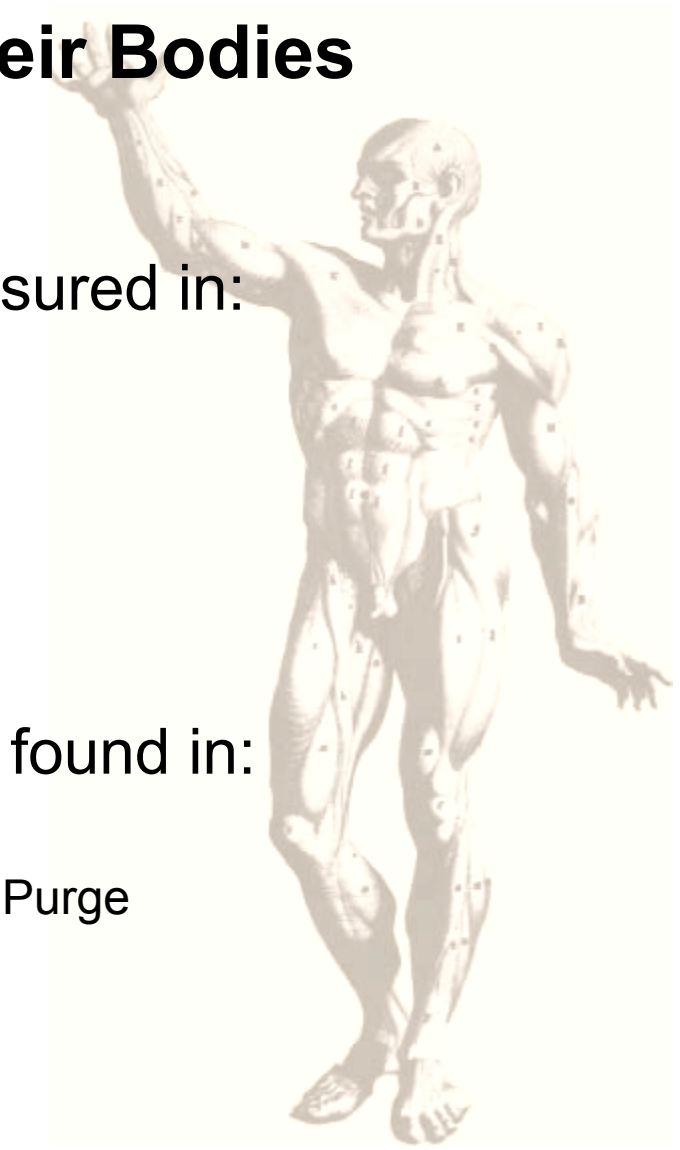
e.g. Cord blood Hg or maternal hair Hg -
proxy for MeHg injested during pregnancy

Summary/Outline

Emerging Evidence of a Subpopulation Extra-Sensitive to Environmental Hg

- The EPA did not consider subpopulations
- A subpopulation of infants was recently discovered with significantly higher Hg in their bodies.
- This subpopulation appears to have a significantly decreased ability to excrete Hg from their bodies, making them extra-sensitive to Hg exposure during their critical neuro-developmental periods.
- This decreased excretion capability is probably genetic
- This has only come to light over the last couple of years

Higher Hg in Their Bodies



Interpreting Hg levels measured in:

- Blood, Urine
- Hair, Toenails, Teeth
- Liver, Kidneys, Heart
- Brain

Let's look at the Hg levels found in:

- Baby Teeth
- Whole-Body Chelation Purge
- Infants' First Hair Cut

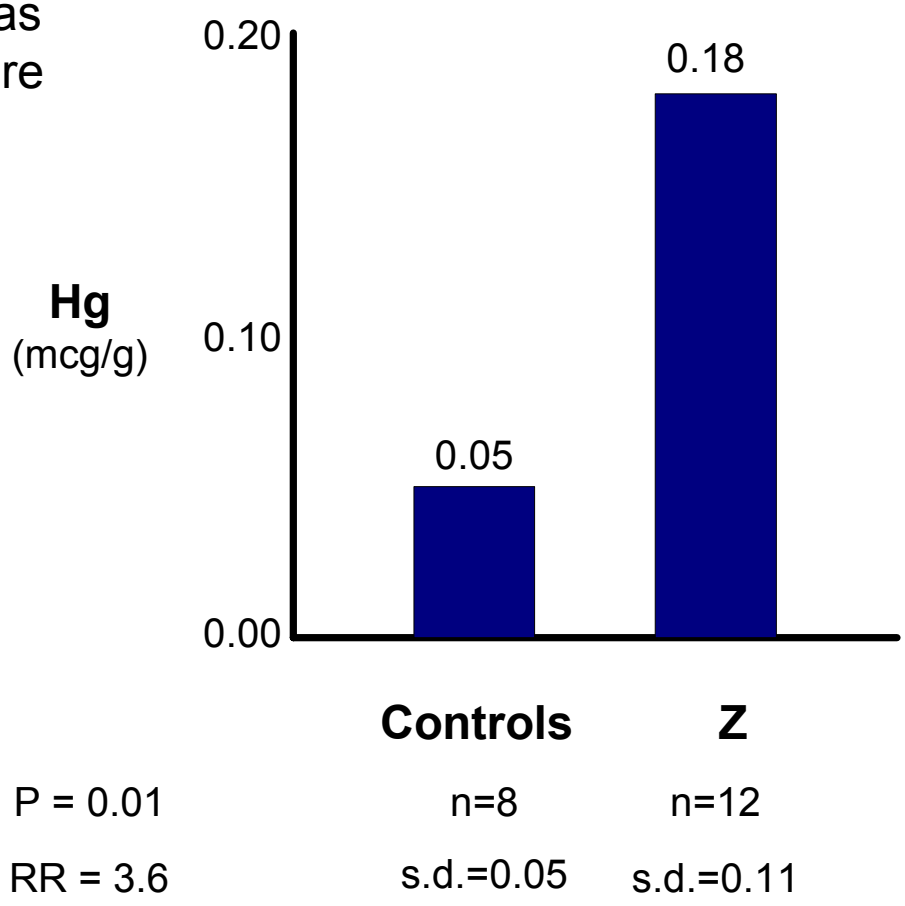
First, a Little Background on Hg in the Body

- In adults, MeHg from eating fish is redistributed to tissues in ~30 hrs with about 5% to blood and 10% across the blood-brain barrier
- MeHg is demethylated to inorganic Hg in the gut by microflora at ~1%/day & in the brain by other means; building up in the body as inorganic Hg
- Inorganic Hg is eventually eliminated primarily through feces
- In adults, typically a latency period between exposure & symptoms
- Hg is highly toxic in humans, particularly to the developing brain
- Hg crosses the placental barrier and is found in breast milk

[Clarkson 2002.]

ASU Pilot Baby-Tooth Study

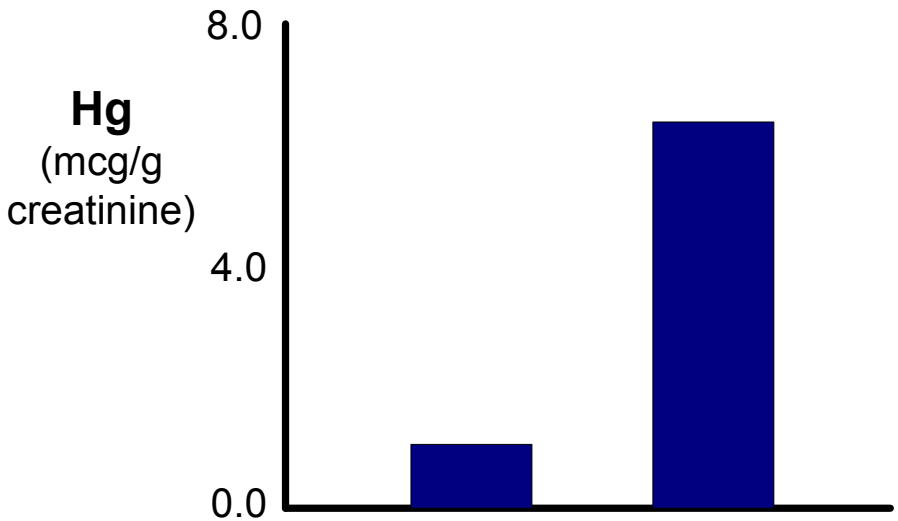
- Lead in baby teeth accepted as best measure of early exposure
- Tooth crown forms during pregnancy, grows until age 4, so records cumulative early body burden
- Children born 1988-99
- **Big, statistically-significant difference in Hg content of Z subpopulation**
- Pb & Zn measured too, but no significant differences



[Adams et al. 2004]

DMSA Chelation Challenge

- 3-15 yrs. old, avg. age 6 yrs.; all vaccinated, no amalgams; Z: n=55, Controls: n=8, age- & sex-matched.
- DMSA is oral chelating agent
- 3-day, 9-dose, 10-mg/kg-dose DMSA treatment, then urine collection & analysis
- **Six-times the Hg was being removed from the Z bodies**
- Pb & Cd: no stat. difference

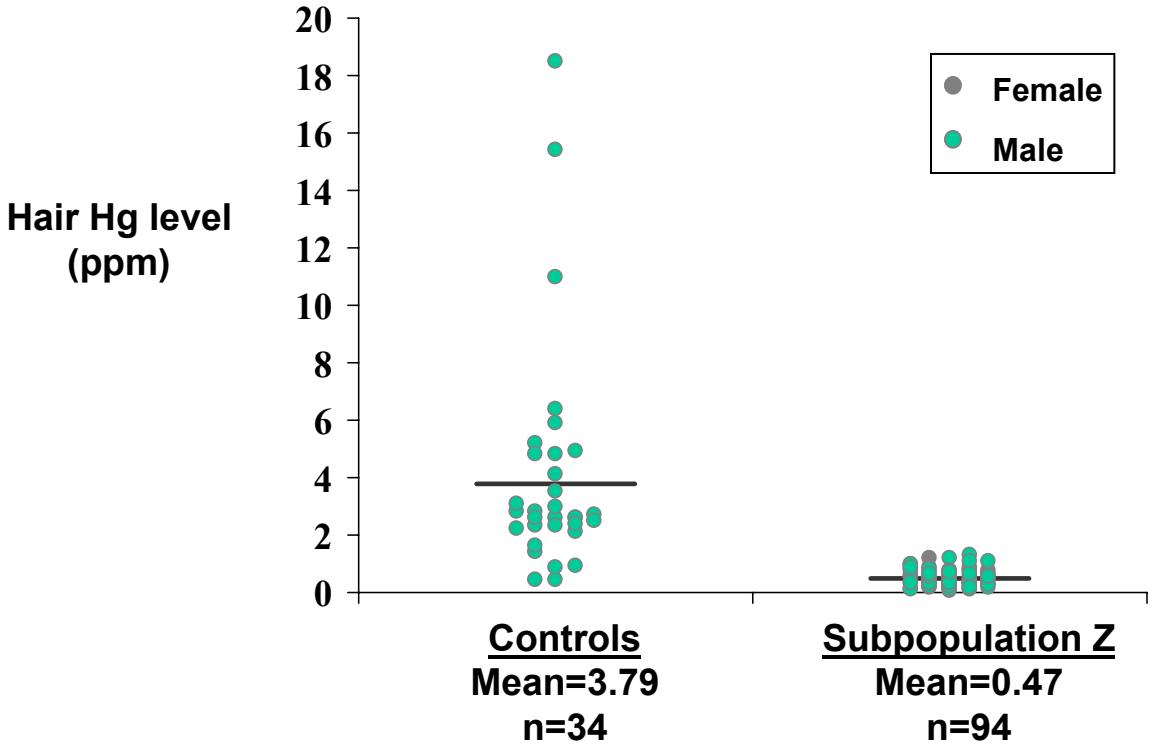


	Controls	Z
P < 0.005	avg=1.1	avg=6.4
RR = 5.9	s.d.=1.1	s.d.=12.7

[Bradstreet, Adams, et al. 2003]

Yet Hair of Z Infants (not Children) Has Less Hg

Hair Hg of Normal Infants vs. Subpopulation Z

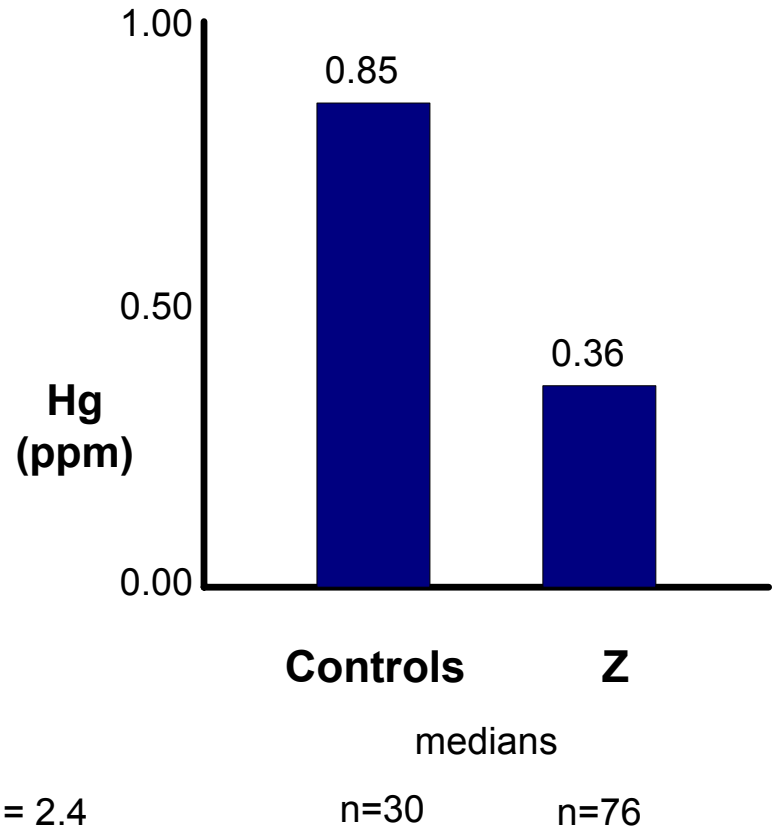


(Note that hair Hg reflects blood Hg, which reflects the body's *excretion* of Hg, *not* its damaging build-up)

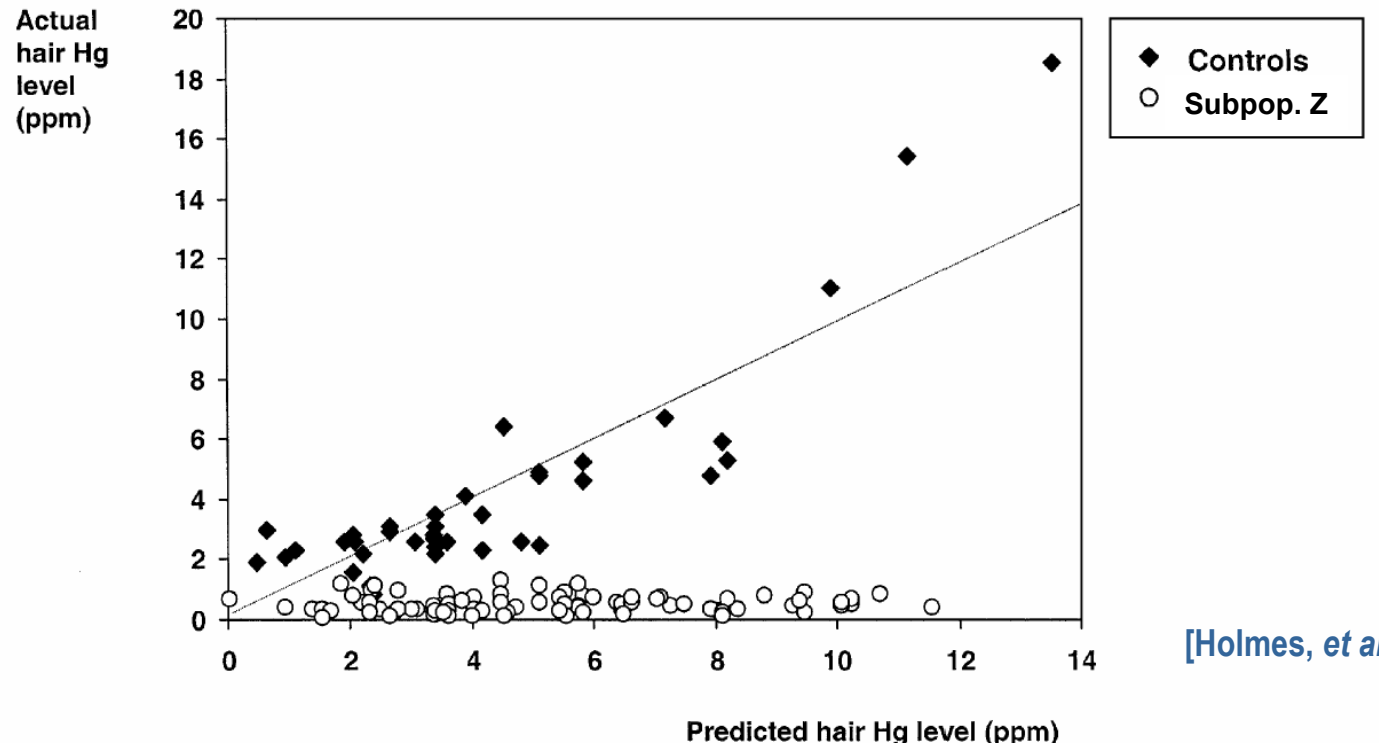
[Holmes, *et al.*, 2002.]

ASU/NIEHS/MIT Infant Hair Replication Study

- Confirms basic Holmes et al. findings, but lower Hg in our Controls
- Average infant age = 15 mo.; all from Arizona
- **Similarly a large difference in Hg content**
- Bimodal Z: while the median Subpop. Z Hg was significantly lower, 10% of Z infants had extremely high Hg (~7 ppm)



Infant Hair Hg Could be Predicted for Normal Babies, - But Not for Those in Subpopulation Z



[Holmes, *et al.*, 2002.]

The predicted value is obtained using the regression equation for Controls:

First-haircut Hg ppm = -5.60 + 0.04 (amalgam volume[1]) + 1.15 (fish consumption[2]) + 0.03 (cum.vaccine[3])

R^2 = 0.79. Statistical significance: [1]=P<0.000000002; [2]=P<0.00002; [3]=P<0.02

ASU Survey of Subpopulation Z

- Z: n=53 children, ages 3-15, from Phoenix area
  Controls: n=48 children, friends (but not related) of Z subpopulation

- Seafood >2 servings/month during pregnancy/breastfeeding?
  Z: 58% vs. Controls: 33%
  Increased risk of Z=2.7x R.R.; p=0.02.

- Number of mother total dental amalgams? Not statistically different.
  Number of mothers' new dental amalgams during pregnancy?
  Z:6 vs. Controls:1; p=0.09 (trend)

- Avg. number of ear infections in first 3 years of life (~antibiotics)?
  Z:11 vs. Controls:4; p=0.00006. Symptom of Z or cause-related?
  (In [Rowland 1984], the half-life for the excretion of Hg in rats given high doses of antibiotics increased from 10 days to >100 days.
  Antibiotics could kill intestinal microflora needed to process MeHg.)

[Adams et al. 2003b]

Conclusion:

Fetuses/infants/children of a minority subpopulation have a much higher body burden of Hg than does the regular population.

Possibilities:

1. The subpopulation of fetuses/infants is exposed to very high Hg;
2. The subpopulation of fetuses/infants cannot excrete Hg well; or
3. A combination of both.

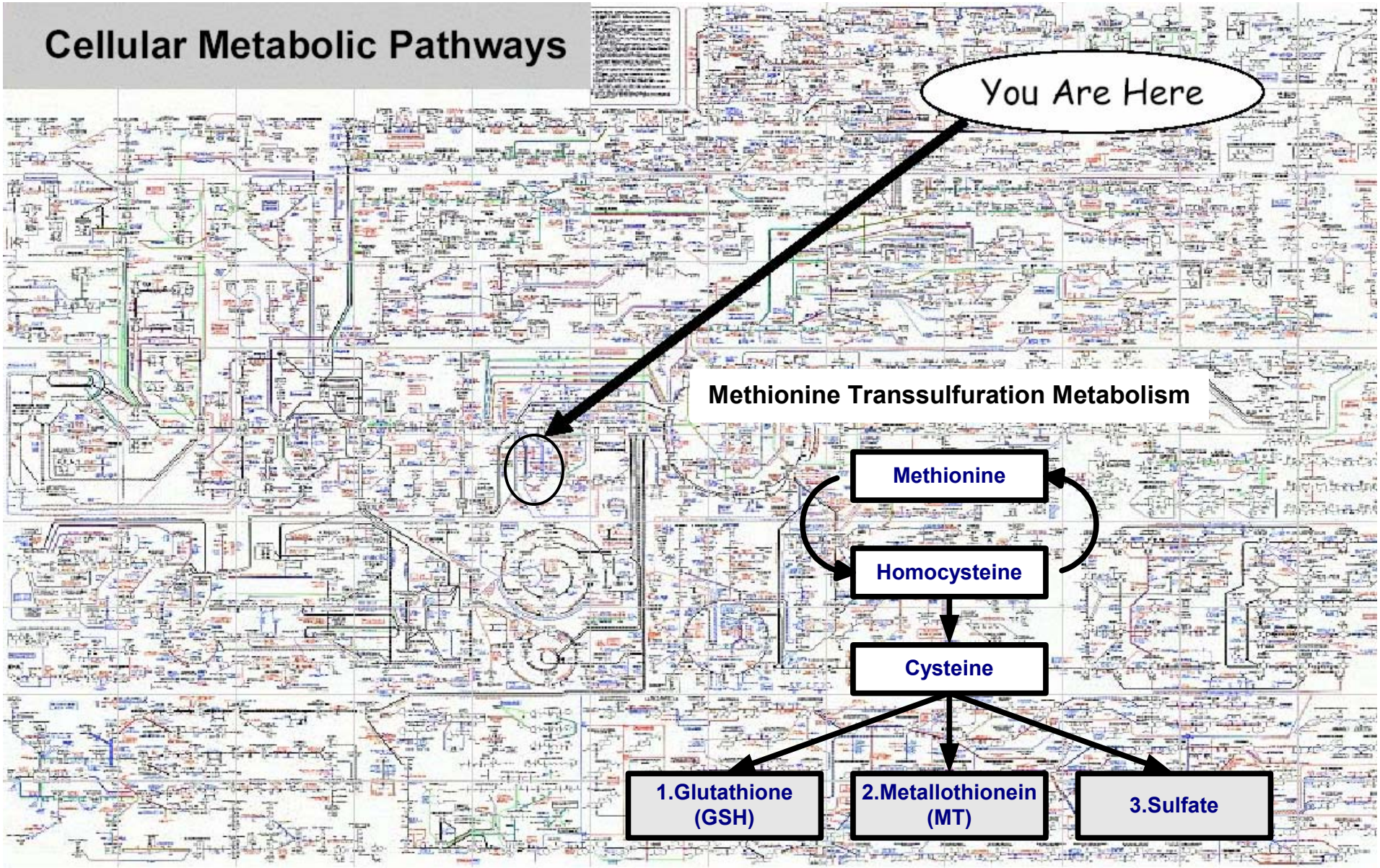
How Do Humans Detoxify their Mercury?

- The metabolism of our bodies use two thiols (reduced S compounds), active **glutathione (GSH)** & metallothionein (MT) to sequester the Hg.
- 95% of ingested Hg, Pb, Cd, etc. is taken up by GSH or MT at the intestinal mucosa.
- 80% of toxic metals entering the blood stream become bound to GSH or MT in the liver.
- 95% of remaining toxic metals are sequestered by GSH or MT at the blood/brain barrier. GSH & MT are also available in the brain.

GSH & MT are the body's sequesterers of heavy metals and once bound, the toxic metals become inactive & are able to be excreted.

[Walsh 2005.]

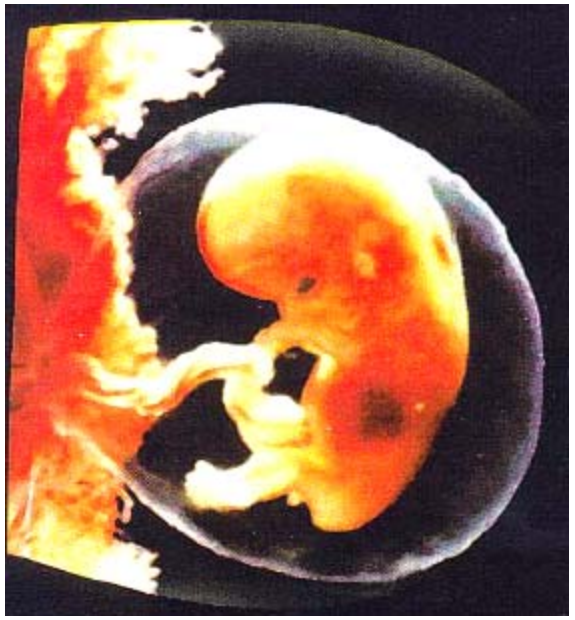
Cellular Metabolic Pathways



[James 2005a]

Timing is Critical: Fetuses or Infants Are Already Extra-Sensitive to Environmental Hg

- No or much-lessened blood/brain barrier
- No or much-lessened intestinal microflora
- No or much-lessened bile production
- Immature immune system/autoimmunity
- Their brains are undergoing massive, critical, intricate construction



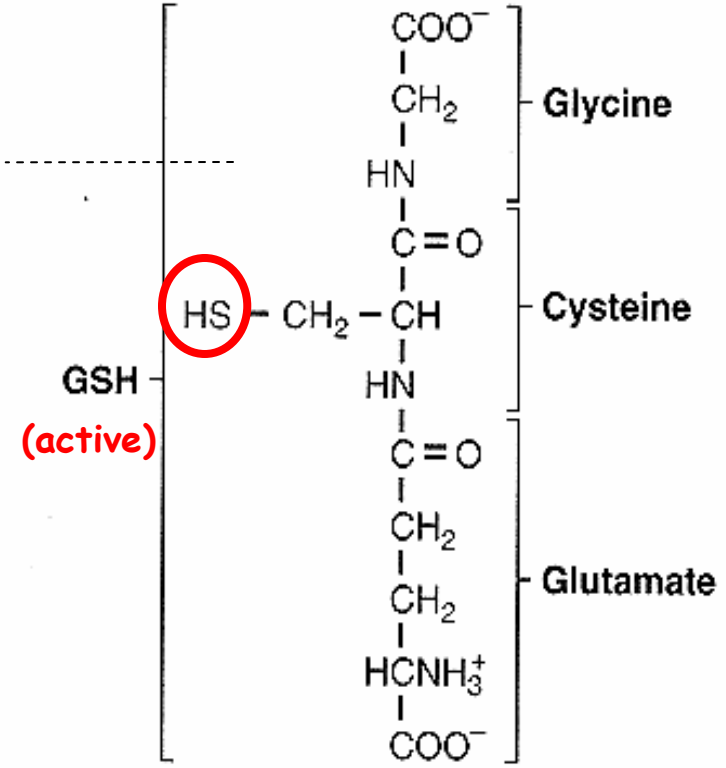
1. Glutathione

DETOXIFICATION FUNCTION OF GLUTATHIONE

Detoxification:
Hg, As, Pb, Cd bind to the thiol (SH) group; then the metal-cysteine conjugate is excreted in bile or urine.

(GSSG = oxidized, inactive)

GSH provides similar cellular protection reacting with species causing "Oxidative Stress" (e.g. O_2^-, H_2O_2, $OH\cdot$)



[James 2005a.]

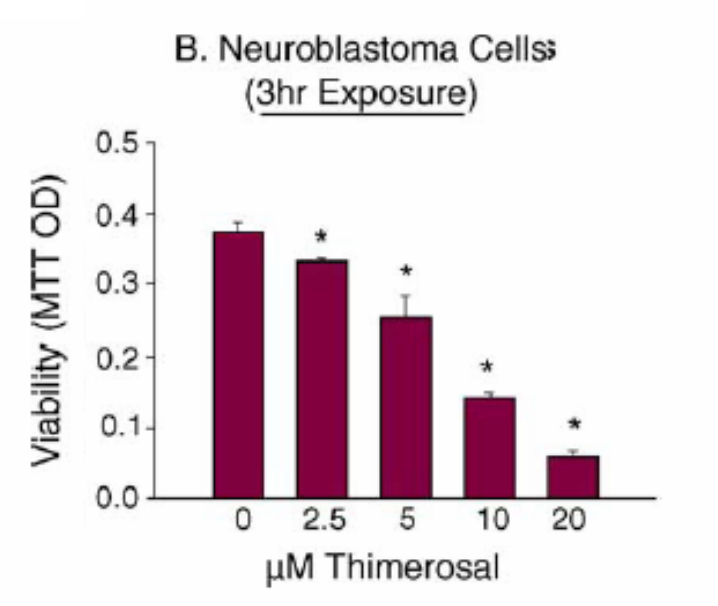
Methionine Cycle & Transsulfuration Metabolites

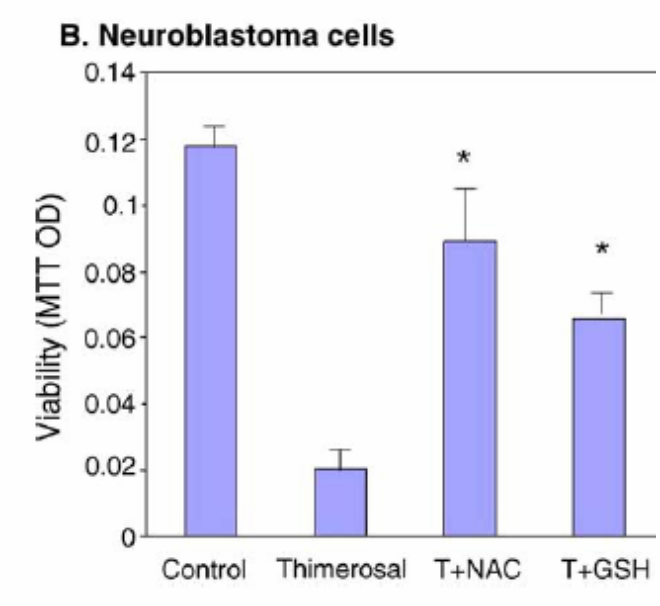
	Control Children n=33	Z Children n=20	p value
Methionine	**31.5**	**19.3**	**0.001**
SAM	96.9	75.8	0.01
SAH	19.4	28.9	0.001
SAM/SAH Ratio	5.2	2.9	0.001
Adenosine	0.27	0.39	0.05
Homocysteine	6.4	5.8	0.01
Cystathionine	0.17	0.14	0.002
Cysteine	202	163	0.001
Total Glutathione	7.6	4.1	0.001
Oxidized (Inactive) Glutathione	0.32	0.55	0.001
GSH/GSSG Ratio (Active/Inactive)	**25.5**	**8.6**	**0.001**

- **Subpopulation Z children have only one-third the active-to-used-up GSH**
- **Significantly deficient metabolism throughout the pathway**

[James, et al. 2004]

Experimental Confirmation





- **EthHg (thimerosal) kills neural cells at micromolar levels; effect similar at even lower levels with longer than a 3 hr exposure**
- **Replacing depleted GSH or cysteine increases neural cell viability**

Thimerosol is 50% ethylmercury. In the second chart, pretreatment of the cells with extra cysteine (NAC = *N*-aceytl cysteine) or glutathione prevented cytotoxicity with exposure to 15 mM ethylmercury. Asterisks in first = $p<0.01$ versus control; asterisks in second = $p<0.05$ vs.thimerosal alone.

[James, *et al.* 2005b.]

2. Sulfate

Significant Sulfate Differences Too

Sulfur metabolism is implicated too. GSH's thiol is a sulfur compound.

Urine Species (in nmol/ml) All p<0.001	Controls n=68 age=8.5	Z Children n=232 age=7.6
Sulfate	3000	6800
Sulfite	2	107
Thiosulfate	19	131
Thiocyanate	44	6

Blood Plasma p<0.001	Controls n=14	Z Children n=14
Sulfate	8.3	1.5

[Waring & Klovrza, 2000.]

Conclusion:

The fetuses/infants/children of this subpopulation have a highly impaired metabolism for sequestering and excreting toxic metals -- making them much more sensitive to environmental mercury insults during their critical neuro-developmental periods -- compared to the majority of the population.

Conclusion:

The fetuses/infants/children of this subpopulation have a highly impaired metabolism for sequestering and excreting toxic metals -- making them much more sensitive to environmental mercury insults during their critical neuro-developmental periods -- compared to the majority of the population.

Question:

Who is this subpopulation? What has happened to them?

Conclusion:

The fetuses/infants/children of this subpopulation have a highly impaired metabolism for sequestering and excreting toxic metals -- making them much more sensitive to environmental mercury insults during their critical neuro-developmental periods -- compared to the majority of the population.

Question:

Who is this subpopulation? What has happened to them?

Answer:

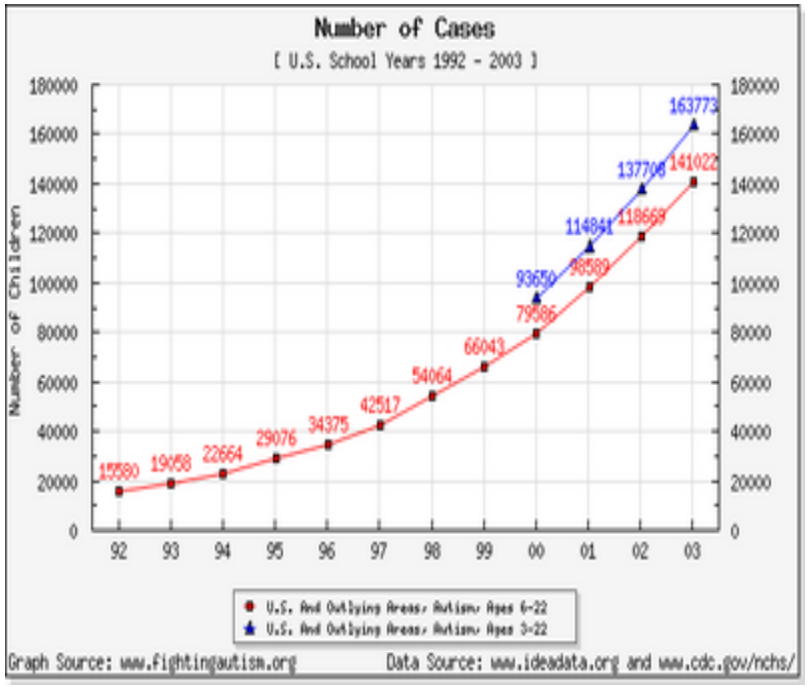
They have become Autistic.

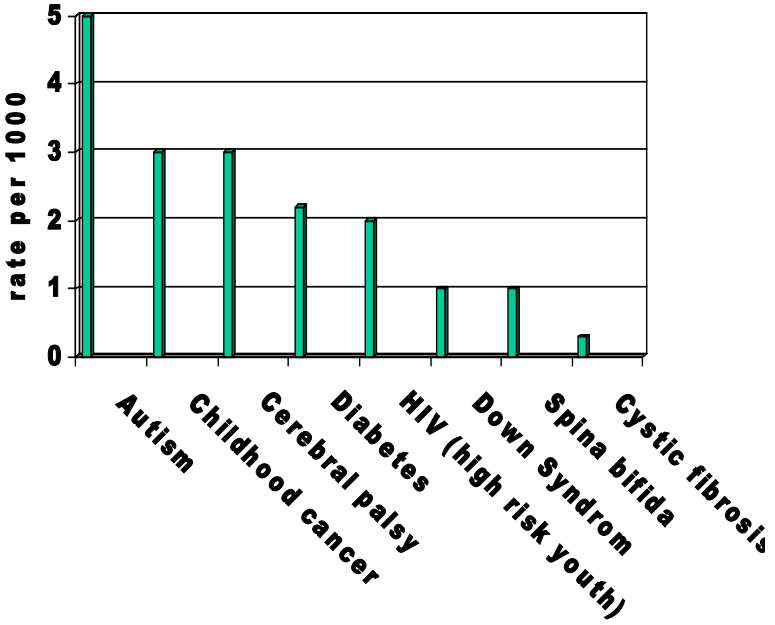
What is Autism or Autism Spectrum Disorder (ASD)?

- Complex neuro-developmental disorder evident in infancy or with an early developmental regression
- Actually a range of disorders (ASD) with autism at one end
- Not diagnosable by physical means, just manifested behaviors

- Commonly characterized by:
  - lack of social reciprocity & responsiveness, social isolation
  - speech repetition or other language abnormalities
  - restricted, repetitive repertoire of activities
  - poor eye contact, hand flapping, tactile defensiveness, etc.
- About 4:1 more common in males

Huge Growth Over the Last 20 Years

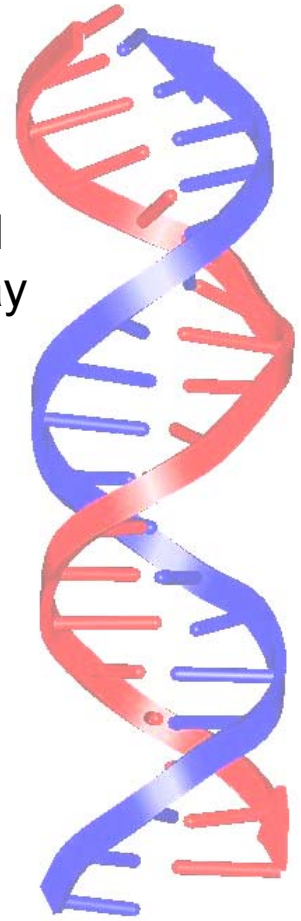




- Medical establishment largely has no clue as to what causes it, other than a genetic predisposition
- But it's impossible to have a genetic epidemic

Genetics & Polymorphisms

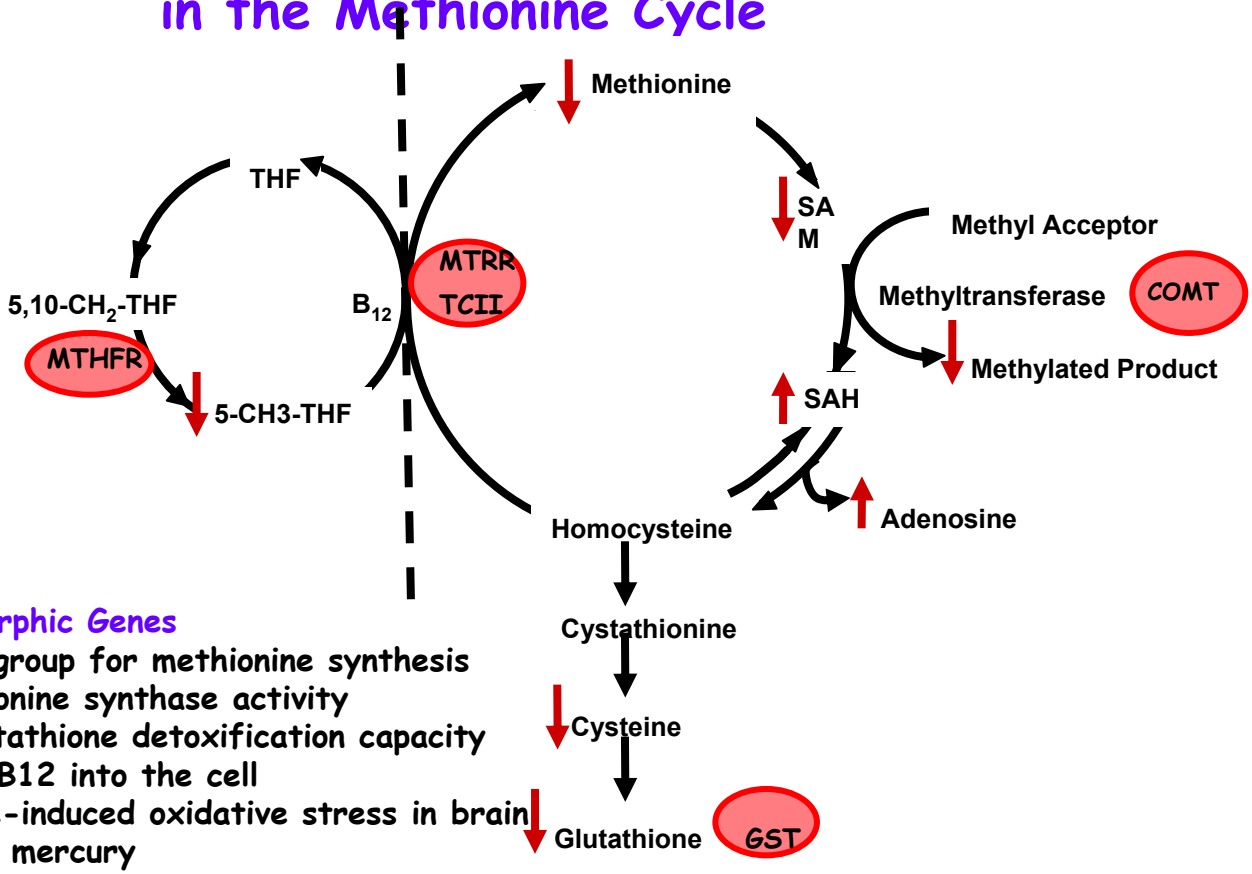
- Co-occurrence in identical twins is 40-70%, but not 100%
- Parents with one autistic child have a 5-10% chance a 2nd child will be autistic & 25% chance for a major speech delay
- No single autism genes has ever been identified; most likely the combined effect of many genes, probably SNPs, combined with an environmental stimulus



Single Nucleotide Polymorphism (SNP) –
A naturally-common single-base-pair variation in a DNA sequence, which can subtly alter the 3-D structure of a protein, more significantly effecting the kinetics of the protein's function

Some Identified Genes Affect Glutathione Metabolism

Metabolic Response to Genetic Polymorphisms in the Methionine Cycle



Functions of Various Polymorphic Genes

MTHFR: Transfers methyl group for methionine synthesis
MTRR: May reduce methionine synthase activity
GSTs: Important for glutathione detoxification capacity
TCII: Transports methylB12 into the cell
COMT: Prevents dopamine-induced oxidative stress in brain
APO E4: May help detoxify mercury

James, J., *et al.*, "Evidence for Increased Oxidative Stress and Impaired Methylation Capacity in Children with Autism: Metabolic Biomarkers and Genetic Predisposition," Amer. Jl. Clinical Nutrition, 80: 611-17, 2004.

An Effort Has Begun to Correlate the Relative Frequencies of Different Alleles

E.g. Polymorphisms Affecting Methylation & Oxidative Stress

Transcobalamin II (TCII 776 66C→G)

(i.e. guanine instead of cytosine at the DNA site)

TCII 776 GG	Frequency	Odds Ratio	p value
Control Individuals (203):	16.0%		
Autistic Children (360):	25.8%	1.8	0.03**

Catechol-O-Methyltransferase (COMT 1947A→G)

COMT 1947GG: (low activity variant)	Frequency	Odds Ratio	p value
Control Individuals (205):	16.3%		
Autistic Children (360):	26%	2.34	0.03**

Combined TCII GG plus COMT GG

TCII GG/COMT GG	Frequency	Odds Ratio	p value
Control Individuals (203):	2.5%		
Autistic Children (360):	9.7%	7.0	0.01**

Is the Mercury the Cause of Autism or a Result?

- **Science tells us that the chemical & physiological effects of Hg on brain development, anatomy, and function are profound.**

(e.g. aberrant neuronal migration, apoptotic neuronal death;
retraction of neuronal contacts, reduction in neuronal mitotic activity)

[Costa et al. 2004.] [Palmen et al. 2004.]

- **Medicine tells us that the manifested symptoms of autism are largely the same as those of mercury poisoning.**

(e.g. language deficits, social withdrawal, mental retardation,
poor coordination, unusual behaviors, higher sensitivity in males)

[Bernard et al. 2001.]

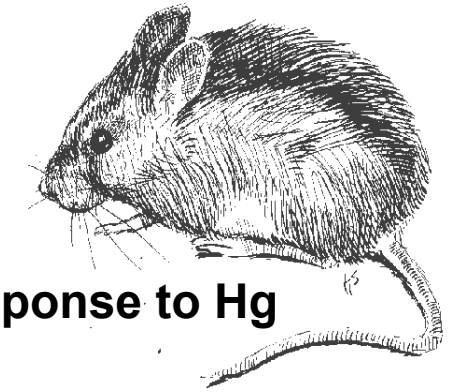
Wrong Genes x Early Hg Exposure

- Mouse Model:
  2 strains genetically resistant to autoimmunity
  1 strain genetically autoimmune disease-sensitive

- Some pups of each given ethylmercury proportional to that given in the 2000 U.S. infant dosing schedule of vaccines

- **Highly statistically-significant differences** were found between the **Hg-exposed** & **non-exposed** mice in:
  - growth delay; reduced locomotion;
  - exaggerated response to novelty;
  - packing of hippocampal neurons;
  - altered glutamate receptors & transport;

  <u>but only</u> in the genetically-sensitive strain



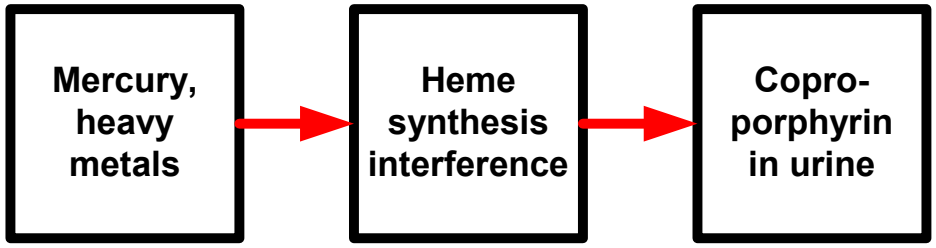
i.e.: differing genes = dramatically different response to Hg

[Hornig et al., 2004]

And Yet More Evidence…

In addition to looking for Hg directly, look for Hg's biological effects, like increased urinary coproporphyrin

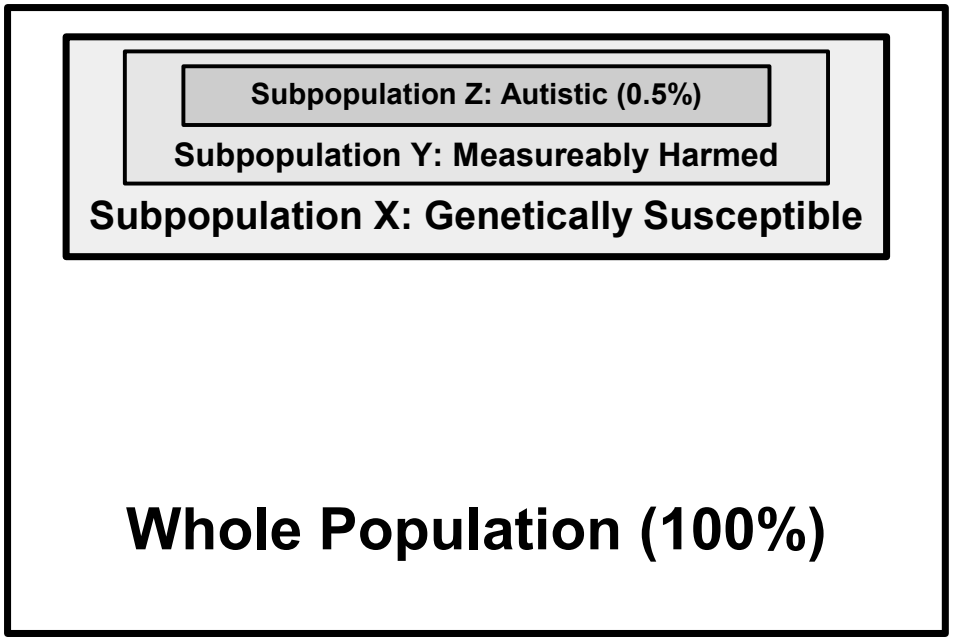
[Woods, J., "Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity," *Canadian Journal of Physiology & Pharmacology,* 74(2):210-215, Feb. 1996.]



In recent measurements on a hundred autistic French children, urinary coproporphyrin averaged 2.6 times that of controls [Nataf 2006] (which translated to about 20X more Hg in [Woods])

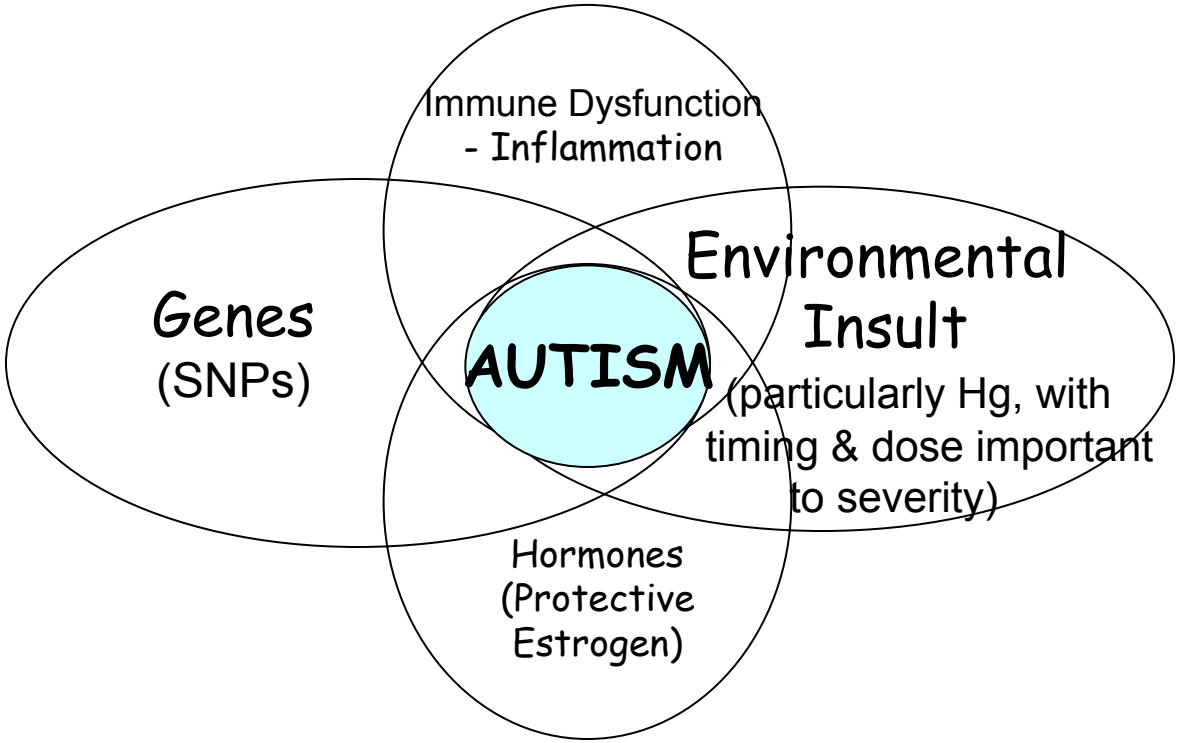
These children are not suffering from autism;
they are suffering from Hg toxicity.

One Way to Think About Autism



Going from Subpopulation X to Subpopulation Y requires an environmental trigger, like exposure to Hg at the wrong time.

Emerging Model of the Cause of Autism & Other Neuro-Developmental Disorders



[Above is adapted from James 2005. This information keeps building. For a good recent summary, see Mutter et al. 2005.]

The Problem is Not Just Vaccine Hg

- **Many vaccines were added to the infant schedule in the 1990s**
- **EthHg was removed from infant vaccines in late 1999-2001**

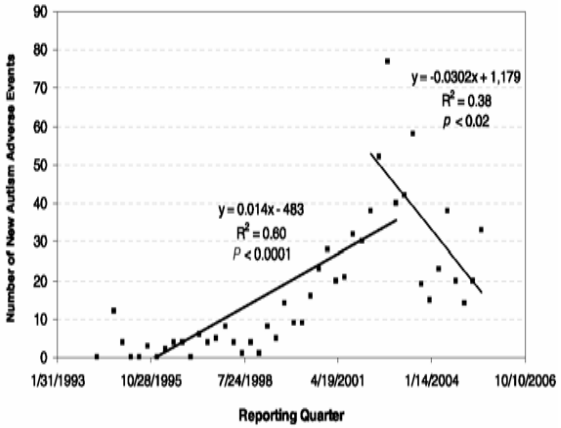


Figure 1. Trends in New Autism Adverse Events Reported to VAERS. The

VAERS=Federal Vaccine Adverse Event Reporting System

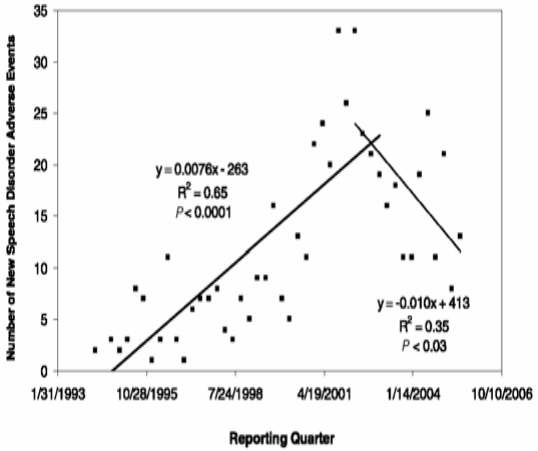


Figure 2. Trends in New Cases of Speech Disorders Reported to VAERS.

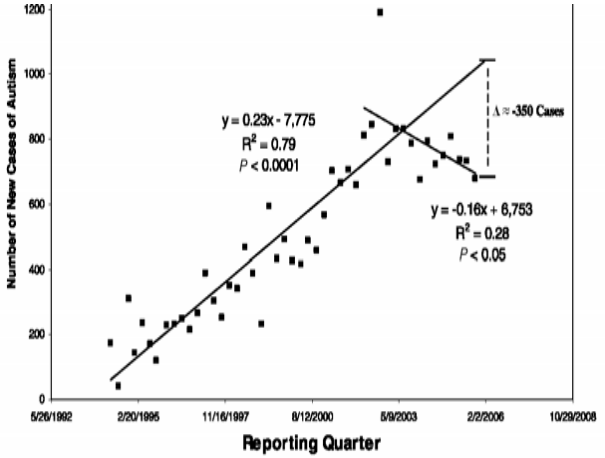


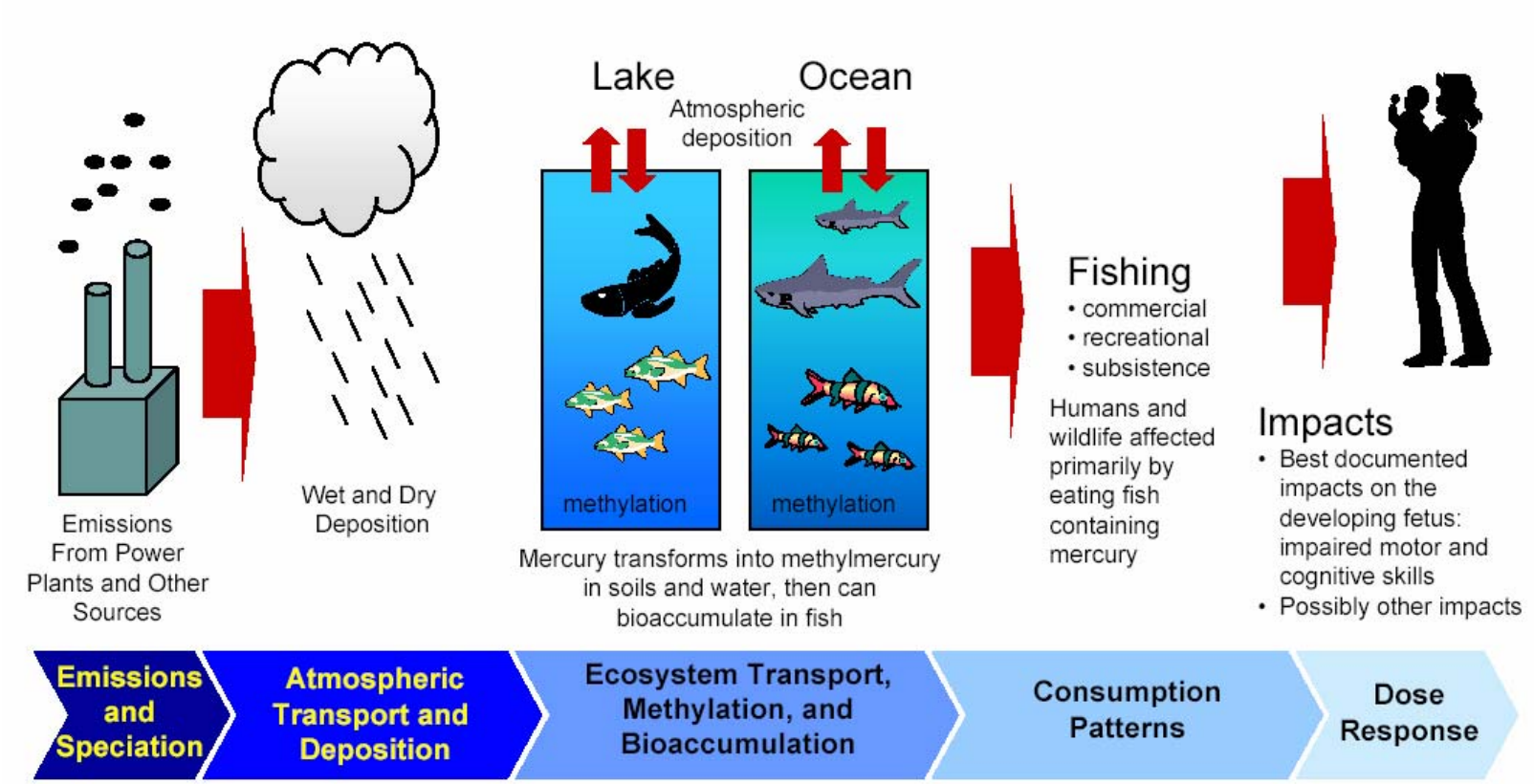
Figure 3. Trends in New Cases of Autism Entered into the CDDS. The trend

CDDS=California Department of Developmental Services

- **Autism & speech disorder cases dropped, but still far from zero**
- **Additional environmental Hg exposure is implicated in autism**

[Geier & Geier, "Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines," *J. Amer. Physicians & Surg.* 11:1, 8-13, 2006.]

Other Exposures: Fish, Power Plants



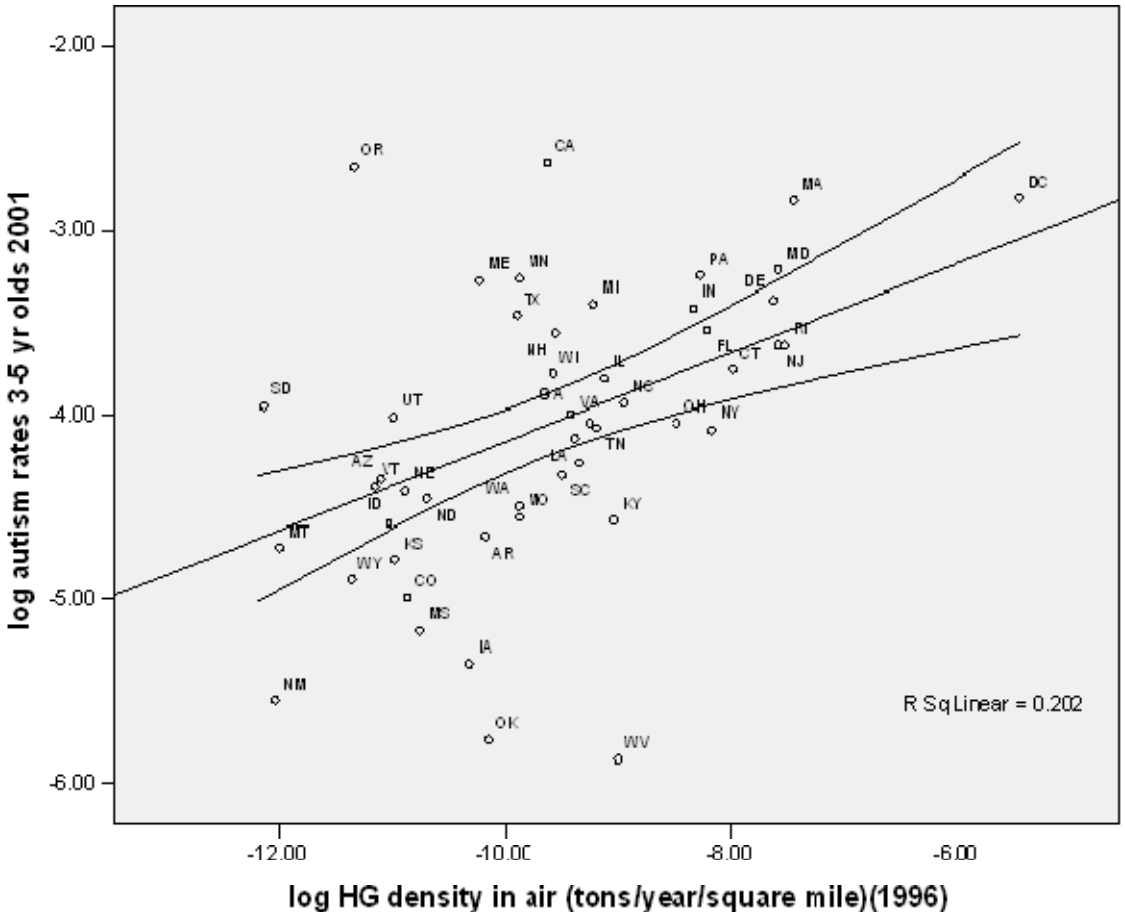
Source: U.S. EPA.

Association of Hg Emissions & Autism

- Recent statistical analysis of the geographical association of Autism cases by school district and industrial Toxic Release Inventory mercury emissions, including power plants, in Texas
- Controlled for urban/suburban/rural district type and wealth
- **For each 1000 lb Hg emitted, found a 60% increase in Autism rate**
- Nearby Hg also explained total district learning-disability expenses
- Study identified Brewster County as an Autism "hot spot" far from Hg emitters. Further investigation revealed it to be the former location of a large Hg mine and Hg ore-roasting furnace

[Palmer, R., *et al.*, "Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas," *Health & Place*, 12:203–209, 2006.]

National Association of Ambient Hg & Autism



- Definite national correlation of EPA state ambient Hg estimates & Autism rates

[Data analysis: Palmer, R., Univ. of Texas Health Science Center, San Antonio Dept. of Family & Community Medicine.]

[Note: Nevada removed due to new 2000 finding that 10 tons per year of Nevada gold smelting Hg emissions moved it from lowest to highest]

Social Costs of Increased Autism

- Recent estimate of the U.S. lifetime direct medical, direct non-medical, and lost productivity costs: $ 3.9 million for each autistic
- At 28 per 1000, U.S. costs of $43 Billion/year,
- not counting the family social toll (e.g. >80% divorce)
- **Decreasing just 10% means >$4 Billion/yr in benefits**
- Doesn't count costs of lesser developmental disabilities (160 per 1000) such as ADD, learning disabilities, etc.

[Ganz, M., "Costs of Autism in the United States," American Public Health Assoc. Annual Meeting, 2005.]

Huge Hg IQ Effects in the U.S. Were Recently Measured

- Hg measured in 135 Boston-area women upon delivery, with their infants' cognition tested at ~6 months of age (RfD ~ 1.0 ppm hair Hg)

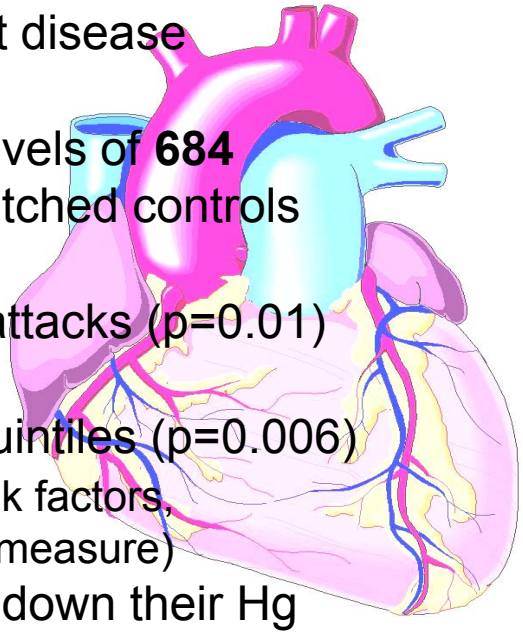
Mean VRM Scores	Maternal hair mercury	
Weekly fish intake	**<1.2** ppm	**>1.2** ppm
> 2 servings	**72** (n= 7)	**55** (n= 2)
< 2 servings	**60** (n= 114)	**53** (n= 12)

- Visual Recognition Memory (VRM) tests correlate with later IQ (r=~0.45)
- Means 10% highest-Hg mothers **lowered their children's IQ ~7 points** (!)
  = r*(SD of IQ/SD of VRM)*ΔVRM = 0.45*(15/7)*(61-53) = 7 IQ points
  [See McCall 1993] & if all women could eat lowered-Hg fish >2x per week, U.S. IQs would be raised ~10 pts. (!) (presumably due to n-3 fatty acids)
- Indicates Hg a critical problem & there is **no** safe Hg dose, as with lead

[Oken, E., *et al*., "Maternal Fish Consumption, Hair Mercury, and Infant Cognition in a U.S. Cohort," *Environmental Health Perspectives*, 113(10):1376, 2005.]

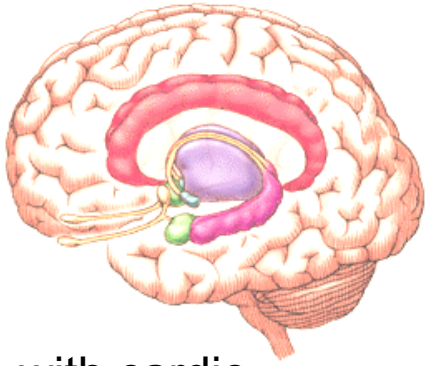
Cardiovascular Deaths & Disabilities

May Also Be a Result of Environmental Hg



- *1 in every 5* U.S. deaths is related to coronary heart disease
- [Guallar et al. 2002] compared the *adult* Hg excretion levels of **684** Europeans suffering first heart attacks with 700 matched controls
- Higher Hg levels were associated with more heart attacks (p=0.01)
- **Relative risk = 2.0** between highest & lowest Hg quintiles (p=0.006)
  (controlling for traditional cardiovascular heart disease risk factors, antioxidant levels, & DHA in adipose tissue as a LT fish measure)
  i.e. we could cut their morbidity by 50% by bringing down their Hg
- Similar recent results in [Virtenan et al. 2005] & in [Yoshizawa et al. 2002] (when Hg-amalgam-exposed dentists removed are from the Yoshizawa sample). See, e.g. [Stern 2005].

But True Effects Could Be Far Greater



- Studies correlating *adult* Hg exposure measurements with cardio-vascular outcomes **will totally miss** sensitive *in utero & infant* limbic autonomic system deficits -- caused by Hg exposure 50+ years earlier -- that could eventually result in the cardiovascular morbidity

  (the "silent neurotoxicity" of Ruehl, see Costa 2004)

- Maternal MeHg was indeed recently shown to permanently affect childrens' sympathetic & parasympathetic modulation of heart-rate variability that is necessary for proper heart function over the long-term

  [Grandjean, P., et al., "Cardia autonomic activity in methylmercury neurotoxicity: 14-year follow-up of Faroese birth cohort," *Journal of Pediatrics*, 2004.]

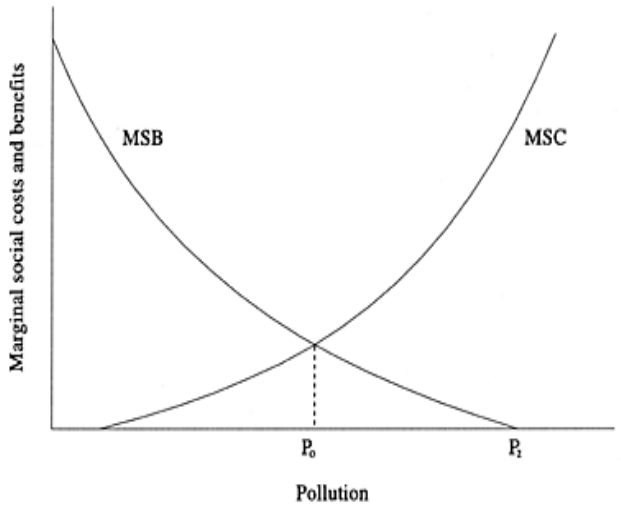
  (See also Murata et al., "Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury," *Jl. Pediatrics*, 2004.)

Mercury May Also Be Responsible for Idiopathic Dilated Cardiomyopathy (IDCM)

- Idiopathic dilated cardiomyopathy (IDCM) with no known cause
- Accounts for nearly 50,000 U.S. hospitalizations & 10,000 U.S. deaths each year
- Analysis of trace elements in myocardial biopsy samples from 13 IDCM patients, compared with 12 patients with valvular heart disease & 13 patients with ischemic heart disease
- Average Hg in IDCM biopsy samples was 22,000 times (!) higher, 178,400 ng/g Hg vs. 8 ng/g
  [Frustaci et al. 1999.]

EPA Cost-Benefit Analysis Supporting CAMR

- Autism Spectrum was *not considered* by the EPA in the RfD determination, nor in their Mercury Rule cost-benefit calculations
- Cardiovascular & IQ effects were *not even considered* either(!)
- Both the EPA's own Inspector General and the GAO have formally & severely criticized the EPA cost-benefit & CAMR outcomes for not even attempting to evaluate the science & economics of CAMR:



"Evidence indicates that EPA senior management instructed EPA staff to develop a MACT standard for mercury that would result in national emissions of 34 tons annually" [!].

"We also found that EPA's rule development process did not comply with certain Agency and Executive Order requirements, including not fully analyzing the cost-benefit of regulatory alternatives and not fully assessing the rule's impact on children's health." - EPA I.G.

"EPA did not estimate the value of the health benefits directly related to decreased mercury emissions" [!] - Government Accountability Office

[U.S. EPA Inspector General 2005 & U.S. GAO 2005.]

How Could the EPA Be *Instructed* on the Results?

End with a riddle:

A **single** state is responsible for **about 40%** of all of the power plant mercury emitted in the United States (and so, the effects of that mercury).

Can you name that state?

Texas? Close, but Wrong

Yes, Texas emits – by far – the most mercury into the environment from coal-fired power plants & its lignites have – by far – the highest Hg – so you would expect Texas energy interests to strongly oppose Hg reductions

But the state responsible for nearly half of U.S. Hg is: **Wyoming**, V.P. Richard Cheney's state, and its Hg leaves in profitable coal cars, not smokestack plumes.

Conclusions

- A subpopulation of infants was recently discovered with significantly higher Hg body burdens.
- This subpopulation has a significantly-decreased ability to excrete Hg from their bodies, making them extra-sensitive to Hg exposure during critical neuro-developmental periods.
- Extreme, unconsidered social costs are involved.
- This new understanding compels us to:
  - lower the MeHg reference dose significantly &
  - lower environmental Hg quickly & dramatically.
- A home-state economic bias infected national Hg policy

Sources

Adams, et al., "Toxic metals and essential minerals in the hair of children with autism and their mothers," 2003a. Available at: http://www.eas.asu.edu/~autism/Research/HairPaper.doc

Adams, et al., "Exposure to heavy metals, physical symptoms, and developmental milestones in children with autism," 2003b. Available at: http://www.eas.asu.edu/~autism/Research/HvyMetalQuestionaire.doc

Autism Research Institute - Defeat Autism Now! (DAN!), Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities: Consensus Position Paper, Feb. 2005.
Available at: http://www.eas.asu.edu/~autism/DANConsensusReport.htm

Bernard, S., et. al. "Autism: A novel type of mercury poisoning," *Medical Hypothesis* 56(4) 462-471 (2001).
Available at: http://www.generationrescue.org/pdf/bernard.pdf

Bradstreet, Adams, et al., "A case-control study of mercury burden in children with autistic spectrum disorders," *Journal of American Physicians and Surgeons*, 8 (3) Summer 76-79, 2003.
Available at: http://www.eas.asu.edu/~autism/Research/MercuryBurdenInAutism.pdf

Burbacher, T., et al., "Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal," *Environ Health Perspectives* 113:1015-21, 2005.
Available at: http://www.safeminds.org/research/library/Burbacher-EHP-Primates-April-2005.pdf

Clarkson, The three modern faces of mercury," *Environmental Health Perspectives* 2002.
Available at: http://ehp.niehs.nih.gov/members/2002/suppl-1/11-23clarkson/EHP110s1p11PDF.pdf

Costa, L., et al., "Developmental neuropathology of environmental agents," *Annu. Rev. Pharmacol. Toxicol.* 44:87–110, 2004.

Frustaci, A., et al., “Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction,” *Jl. Amer. Coll. Cardiology*, 33:6, 1578 1999.

Geier & Geier, “Early downward trends in neurodevelopmental disorders following removal of Thimerosal-containing vaccines,” *J. Amer. Physicians & Surg.* 11:1, 8-13, 2006. Available at: http://www.a-champ.org/documents/geier%20Early%20Downward%20Trends%20JAPS%203-1-06.pdf

Guallar, E.., et al., “Mercury, fish oils, and the risk of myocardial infarction,” *New England Journal of Medicine*, 347:1747-1754, 2002.

Grandjean, P., et al., “Cardia autonomic activity in methylmercury neurotoxicity: 14 year follow-up of Faroese birth cohort,” *Journal of Pediatrics*, 2004.

Holmes, A., et al., “Reduced levels of mercury in first baby haircuts of autistic children,” *Int. J. Toxicol.* 22(4):277-85, 2003. Available at: http://www.momsonamissionforautism.org/mercury/final.article.pdf

Hornig, M., et al., “Neurotoxic effects of postnatal thimerosal are mouse strain dependent,” *Molecular Psychiatry*, 1–13, 2004. Available at: http://www.greeneidlab.columbia.edu/press_releases/Strain-dep-thimerosal.pdf

James, S. J., et al., “Evidence for increased oxidative stress and impaired methylation capacity in children with autism: metabolic biomarkers and genetic predisposition,” *Amer. Jl. Clin. Nutrition*, 80: 611-17, 2004b

James, S. J., “Pathogenic Implications of Low Glutathione Levels and Oxidative Stress in Children with Autism: Metabolic Biomarkers and Genetic Predisposition,” presentation at Autism One Conference, May 2005a. Available at: http://autismone.org/AutismOne2005/uploads/James Jill.ppt.

James, S. J. et al., “Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors,” *NeuroToxicology*, 26:1–8, 2005b.

Nataf, R., et al., “Porphyrinuria in childhood autistic disorder: Implications for environmental toxicity,” *Toxicology and Applied Pharmacology*, 2006. In Press. Available at: http://www.safeminds.org/pressroom/pres_releases/060504-NATAF2006final.pdf

Mahaffey, K., U.S. EPA, “Methylmercury: Epidemiology Update,” Fish Forum, San Diego, 2004. Available at: www.epa.gov/waterscience/fish/forum/2004/presentations/monday/mahaffey.pdf

McCall & Carriger, “A meta-analysis of infant habituation and recognition memory performance as predictors of later IQ,” *Child Development*, 64:57-79, 1993.

Murata, K., et al., “Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury,” *Journal of Pediatrics* 10:177-183, 2004.

Mutter, J., et al., “Mercury and autism: accelerating evidence?” *Neuroendocrinology Letters*, 26(5):439-446, 2005. Available at: www.generationrescue.org/pdf/mutter.pdf

National Research Council, National Academy of Sciences (NAS), Toxicological Effects of Methyl Mercury, 9 (2000). Available at: http://books.nap.edu/openbook/0309071402/html/index.html

Oken, et al., “Maternal fish consumption, hair mercury, and infant cognition in a U.S. cohort,” 113(10):1376, *Environ. Health Persp.*, Oct. 2005. http://www.pubmedcentral.gov/picrender.fcgi?artid=1281283&blobtype=pdf

Palmen, S., et al., Neuropathological findings in autism,” *Brain*, 127, 2572-2583, 2004.

Palmer, R., et al., “Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas,” *Health & Place*, 12:203–209, 2006.

Rice, “The US EPA reference dose for methylmercury: sources of uncertainty,” *Environ. Res.* 95:406, 2004.

Rowland, I., *et al.*, “Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora.,” *Arch. Environ. Health.* 39:6, 401-408, 1984.

Stern, A., “A review of the studies of the cardiovascular health effects of methylmercury with consideration of their suitability for risk assessment,” *Environmental Research*, 98(1):133-42, 2005.

U.S. EPA, “Water Quality Criterion for the Protection of Human Health: Methylmercury,” EPA-823-R-01-001 January 2001. Available at: http://www.epa.gov/waterscience/criteria/methylmercury/document.html

U.S. EPA, Inspector General Evaluation Report, “Additional Analyses of Mercury Emissions Needed Before EPA Finalizes Rules for Coal-Fired Electric Utilities,” Report No. 2005-P-00003, February 3, 2005. Available at: www.epa.gov/oig/reports/2005/20050203-2005-P-00003.pdf

U.S. GAO, Report to Congressional Requesters, Clean Air Act Observations on EPA’s Cost-Benefit Analysis of Its Mercury Control Options, GAO-05-252, February 2005. Available at: http://www.gao.gov/new.items/d05252.pdf

Virtenan, J., *et al.*, “Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland,’ *Arterio. Thromb. Vasc. Biol.* 25:228, 2005.

Walsh, W., “Oxidative Stress & Autism: A Roadmap for Effective Treatment,” presentation at Autism One Conference, May 2005. Available at: http://autismone.org/AutismOne2005/uploads/Walsh William.ppt

Waring & Klovrza, “Sulfur metabolism in autism,” *Jl. Nutritional & Environmental Medicine*, 10:25-32, 2000.

Woods, J., “Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity,” *Canadian Journal of Physiology & Pharmacology*, 74(2):210-215, Feb. 1996.